Election/Restriction

Applicants acknowledge that the restriction requirement has been made final.

Claim Rejections under 35 U.S.C. §112 ¶1

Claims 7-9, 11-17, and 21-25 have been rejected under 35 U.S.C. §112 ¶1. Applicants respectfully traverse, since the specification fully enables the amended claims.

A. The Legal Standard

Under 35 U.S.C. §112 ¶ 1, a patent specification containing a teaching of how to make and use the invention must be taken as enabling unless the PTO provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971).

The claimed invention as disclosed in the specification cannot be questioned on the unsupported skepticism of the Office. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant in the disclosure is "enabling" and set forth the "best mode contemplated." Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *ML T v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification

provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); In re *Jackson*, 217 U.S.P.Q. 804, 807 (PTO Pt. Bd. App. Int. 1982) (emphasis added). Finally, the Office has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

B. Meeting the Legal Standard

The claimed invention is directed to methods of protecting therapeutic peptides sensitive to peptidase degradation from peptidase degradation. The peptide is modified with a reactive group and forms a covalent bond between the reactive group and a blood component, thereby protecting the peptide from peptidase degradation. The claimed invention, therefore, is platform technology that facilitates maintaining therapeutic peptide activity.

The Specification provides considerable direction and guidance to one of skill in the art on how to perform the claimed method.

The breadth of the claimed invention is limited to modifying therapeutic peptides of specified length at known positions. First, independent claim 7 is restricted to a method that is

applicable only to peptides containing 3-50 amino acids. Second, the peptides are restricted to those susceptible to peptidase degradation *in vivo*. Peptides vulnerable to peptidase degradation may be determined easily by one of ordinary skill in the art as discussed in the Specification (page 10, line 32 through page 11, line 1 and page 69, line 30 through page 71, line 8).

Further, the nature of the claimed invention is not directed to disclosing new peptides. Rather, the invention is directed to methods for protecting therapeutic peptides against peptidase degradation. The presently claimed methods are not for the purpose of investigating or determining the therapeutic effect of a given peptide. The invention is also not directed to a method of medical treatment of patients.

Both therapeutic peptides and peptidases are well-known in the art. One thousand, six hundred seventeen peptides known in the art are listed and discussed in the Specification (pages 16 through 55). Further, peptidases are well-known enzymes that cleave specific amino acid - amino acid combinations or bonds. For example, a given peptidase may cleave all glutamine-leucine bonds it encounters. Peptidases are well studied, and peptidases nomenclature, based on specificity, exists. Further, numerous peptidases are available commercially.

Peptides susceptible to degradation may be predicted without undue experimentation. For example, conventional modeling software can be used to determine whether a peptide is susceptible to degradation. Alternately, the peptide can be labeled in a conventional manner, and its activity followed until it disappears. An undetectable or very short period of activity clearly indicates the susceptibility of a peptide to peptidase degradation. Both of these techniques are standard and well known in the field, and cannot be considered as "undue experimentation," as alleged by the Office.

Applicants provide substantial direction, guidance, and examples necessary to show one skilled in the art how to perform the claimed methods. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). In the present case, Applicants provide extensive discussion as to the number of known therapeutic peptides (Specification, page 10 line 19 through page 13, line 15). Further, the specification lists an extensive list of known, and extensively studied, therapeutic peptides (Specification, page 11 line 27 through page 13, line 9). The Specification provides 1,617 sequences corresponding to known therapeutic peptides, along with discussion of the structure and function of their therapeutic qualities (Specification, page 13, line 16 through page 55, line 16). The Specification further provides multiple methods of modifying therapeutic peptides. The Specification also provides 70 examples showing modification of therapeutic peptides.

C. Specific Arguments Raised by the Office

Notwithstanding the guidance and direction given by Applicants, the Office has made a number of contentions that are unsupported, particularly in light of the amended claims. The Office argues that the Specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation.

First, the Office alleges that "the specification fails to enable the skilled artisan to practice the invention without undue experimentation wherein patients susceptible to having symptoms of a disorder or dysfunction are treated with the claimed invention." (Office Action, page 3, second paragraph). The presently claimed method does not claim methods of investigating or determining the therapeutic effect of a given peptide. Rather, the therapeutic properties of the protected peptide would protected against peptidase degradation. The invention

is not directed to a method of treating patients. Therefore, Applicants need not disclose methods of efficient medical treatment medical treatment, as implied by the Office.

Second, the Office alleges that although the specification enables protein sequences in Examples 1-70, the specification does not reasonably provide enablement for all peptides composed of between 3 and 50 amino acids that are stabilized against any and all peptidases. A disclosure which contains representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim will possess the alleged utility is all that is required, when there is no reason to suspect the assertions are not accurate. *In re Barr et al.* (CCPA 1971) 444 F.2d 558, 170 USPQ 330. The Office provided no objective evidence to counter Applicants' claims.

The Office seems to insist that the specification should contain a synthesis example for every single peptide comprising between 3 and 50 amino acids. The specification provides for numerous examples of peptides susceptible to peptidase degradation, and comprising between 6 (examples 51-54) and 40 (examples 30-33) amino acids. As stated previously and reiterated here, independent claim 7 is restricted to a method that is applicable only to peptides containing 3-50 amino acids, and susceptible to peptidase degradation *in vivo*. Further, Applicants disclose a large number of known therapeutic peptides (Specification, page 10 line 19 through page 13, line 15, especially page 11 line 27 through page 13, line 9), 1,617 different sequences corresponding to known therapeutic peptides, multiple methods of modifying therapeutic peptides, and 70 examples showing modification of therapeutic peptides.

The Office further asserts that, while a skilled artisan would be motivated to modify proteins of Examples 1-70, the artisan would not know what other proteins or peptidases Applicant is referring to or which would be compatible with the claimed invention. The Office

alleges that the skilled artisan would be forced to test, at random, various proteins in combination with various peptidases to determine which proteins can be modified to form a protein stabilized from peptidase degradation. Applicants, however, need not provide a specific example of everything embraced by a broad claim. *In re Anderson* (CCPA 1973) 471 F.2d 1237, 176 USPQ 331. Indeed, enablement is not precluded by the need for some experimentation such as routine screening. *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). First, as pointed out repeatedly above, the Specification provides an extensive discussion of the known therapeutic peptides, provides nearly 2 pages of known therapeutic peptides, provides an enormous number of sequences corresponding to the peptides, and provides over 70 examples. Second, the claims do not depend on individual peptides. It is well known that peptidases degrade peptides. The present method significantly slows down peptidase activity, while surprisingly retaining its beneficial therapeutic effect.

Since Applicants provided overwhelming support enabling one of skill in the art to follow the claimed methods, Applicants respectfully request that the instant rejection be withdrawn.

Claim Rejections under 35 U.S.C. §112 ¶2

Claims 1-5, 7-9, 11-17, and 21-25 have been rejected on multiple grounds under 35 U.S.C. §112 ¶2 as indefinite for failing to particularly point out or distinctly claim the invention.

(i) Functional Limitations of Peptides

The Office alleges that claims 1-5, 7-9, 11-17, and 21-25 are indefinite because the peptides are not defined with any chemical or physical characteristic, but only by functional properties. The Office asserts that a claim to a material defined solely in terms of what it can do, or a property thereof, does not particularly point out the claimed invention.

First, Applicants define the claimed peptides having lengths between 3 and 50 amino acids. This represents a significant structural limitation of term "peptide." Second, the basic chemical structure of peptides is well known in the art. Third, Applicants are claiming a method of protecting peptides from peptidase degradation, not the peptides themselves. The peptides are therefore claimed using a combination of both structure and functional characteristics.

In light of the foregoing, Applicants submit that the rejection is without basis. Applicants therefore respectfully request that this rejection be withdrawn.

(ii) "Capable of"

The Office has rejected claim 1, asserting that the term "capable of" is vague and indefinite. The Office alleges that the recitation that an element "capable of" performing a function is not a positive limitation, since it requires only the ability to perform a function, and is therefore not a limitation in any patentable sense.

Applicants respectfully traverse this rejection. However, claim 1 has been cancelled without prejudice or disclaimer, rendering this ground for rejection moot. Applicants therefore respectfully request that this rejection be withdrawn.

(iii) "Stabilized"

The Office has rejected claim 1, asserting that that it is not clear what "stabilized" means.

Applicants respectfully traverse this rejection. Specifically, the Specification provides extensive discussion of peptidase stabilized therapeutic peptides, for example, at page 10, lines 1-17.

Claim 1, however, has been cancelled without prejudice or disclaimer, rendering this ground for rejection moot. Applicants therefore respectfully request that this rejection be withdrawn.

(iv) "Therapeutically active region" and "less therapeutically active region"

The Office has rejected claims 1, 2, 3, 4, 5, and 16 as vague and indefinite. The Office alleges that the terms "therapeutically active region" and "less therapeutically active region" are not defined in the specification and that one of ordinary skill in the art would not be apprised of them. Specifically, the Office questions what defines an area that is therapeutically active versus one that is not, and how one area is less active than another.

Regarding claims 1-5, Applicants respectfully traverse this rejection. Claims 1-5, however, have been cancelled without prejudice or disclaimer, rendering this ground for rejection moot. Applicants therefore respectfully request that this rejection be withdrawn.

Regarding claim 16, the expressions "therapeutically active region" and "less therapeutically active region" are neither vague nor indefinite to the skilled artisan, who is well aware that peptides contain a therapeutically active portion, and a less active portion. In fact, nearly two pages of the specification are dedicated to listing therapeutic peptides that are well-known in the art (Specification, page 11, line 27 through page 13, line 9). Consequently, it is standard practice to initially make modification and/or mutation to a peptide as far as possible from the therapeutically active region, to minimize negative effects on the therapeutically active portion thereof.

In addition to knowledge readily available to one of ordinary skill, the Specification provides extensive discussion of therapeutically active regions, therapeutic peptides, and therapeutic activity from page 10, line 19 through page 13, line 14. In particular, beginning at page 10, line 29, the specification discusses therapeutically active regions within modified therapeutic peptides. The Specification further provides guidance for identification of therapeutically active region "using blind or structural activity relationship (SAR) driven

substitution (Specification, page 10 line 32 through page 11, line 1)." SAR is defined even more fully in the Specification from page 69, line 30 to page 71, line 8. In addition, the Specification provides that "the therapeutically active region ...may be obtained by referring to references such as scientific journals (Specification page 11 lines 4-6)." The Specification further defines modification of therapeutic peptides in terms of the therapeutically active region. The "less therapeutically active region" is defined as the region "located away from the therapeutically active region, such that the modification at the less therapeutically active region does not substantially affect the therapeutic activity of the therapeutic peptide (Specification page 11, lines 15-18)." Finally, the Specification provides a detailed list of several known therapeutic peptides having therapeutic activity (Specification, page 11, line 27 through page 13, line 9).

(v) "Stable"

The Office has rejected claim 1, alleging that the term "stable" is a relative term that renders the claim indefinite.

Applicants respectfully traverse this rejection. . Specifically, the Specification provides extensive discussion of peptidase stabilized therapeutic peptides, for example, at page 10, lines 1-17.

Claim 1, however, has been cancelled without prejudice or disclaimer, rendering this ground for rejection moot. Applicants therefore respectfully request that this rejection be withdrawn.

(vi) "Succinimidyl and maleimido groups"

The Office has rejected claim 1, alleging that the term "succinimidyl and maleimido groups" is vague and indefinite, and that it is not clear what compounds are encompassed by the term "groups."

Applicants respectfully traverse this rejection. However, claim 1 has been cancelled without prejudice or disclaimer, rendering this ground for rejection moot. Applicants therefore respectfully request that this rejection be withdrawn.

(vii) "amino acid amino acid"

The Office asserts that claim 7, line 4, reads "amino acid amino acid." It appears from our records, however, that claim 7 reads "amino terminal amino acid." In addition, the claims accompanying this action read "amino terminal amino acid."

However, should the Examiner's version of claim 7 read "amino acid amino acid," Applicants authorize the Examiner to change the claim language to "amino terminal amino acid" by Examiner's Amendment.

Accordingly, this ground for rejection appears to be without basis. Applicants therefore respectfully request that this rejection be withdrawn.

(viii) "reactive functionality on a blood component"

The Office has rejected claims 7 and 16, alleging that the term "reactive functionality on a blood component" is vague and indefinite. Specifically, the Office alleges that it is not clear what the limitation refers to, and suggests that the functionality could be a compound, protein, DNA molecule, blood component, hormone, cell, or blood vessel.

Applicants respectfully traverse this rejection. The specification provides ample definition and support for the term "reactive functionality on a blood component."

First, the specification defines "reactive groups" beginning on page 7, line 21. Specifically, "reactive groups are coupled or bonded to a therapeutic peptide of interest." In addition, the definition provided in the specification additionally lists a number of functional groups at page 7, lines 23-31.

Second, the specification defines "functionalities" beginning on page 8, line 1 of the specification. Specifically,

> "functionalities are groups on blood components, including mobile and fixed proteins, to which reactive groups on modified therapeutic peptides react to form covalent bonds. Functionalities usually include hydroxyl groups for bonding to ester reactive groups, thiol groups for bonding to maleimides, imidates and thioester groups; amino groups for bonding to active carboxyl, phosphoryl or any other acyl groups on reactive groups."

Third, the specification defines "blood components" beginning at page 8, line 10 of the specification. Specifically, blood components "may be either fixed or mobile." "Fixed blood components" include a number of non-mobile blood components listed on page 8, lines 12-17. "Mobile blood components" do not have a fixed situs for any extended period of time, and are further defined at page 8, lines 19-24.

Since the Specification particularly defines "reactive groups," "functionalites," and "blood components," a skilled artisan would readily appreciate the meaning and scope of the limitation "reactive functionality on a blood component."

Applicants therefore respectfully request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. §103(a)

Claims 1-5, 7-9, 11-17, and 21-25 have been rejected over Pouletty *et al.* (WO 95/10302) in view of Oppenhelm *et al.* (U.S. Patent No. 5,837,247).

35 U.S.C. § 103(a) requires that "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The prima facie case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with

general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

1. The Claimed Invention

As amended, independent claim 7 is drawn to a method for protecting a therapeutic peptide sensitive to peptide degradation *in vivo* from peptidase degradation. The peptide comprises between 3 and 50 amino acids. The peptide is protected by coupling a reactive group to the carboxy terminal amino acid, to the amino terminal amino acid, or to an amino acid located between the amino terminal amino acid and the carboxy terminal amino acid of the peptide, and forming a covalent bond between the reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate.

Dependent claims are directed to forming the peptide-blood component conjugate *in vivo* or ex vivo, forming the conjugate using a maleimide reactive group, coupling reactive group to the peptide via a lysine and/or linking group, coupling the peptide to albumin, and having one or more of the amino acids in the peptide be synthetic.

As amended, independent claim 15 is drawn to a method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*. The peptide comprising between 3 and 50 amino acids and has a therapeutically active region of amino acids and a less therapeutically active region of amino acids. The method comprises identifying said therapeutically active region of amino acids, modifying said peptide at an amino acid included in said less therapeutically active region by coupling thereto a reactive group to said amino acid to form a modified peptide, such that said modified peptide has therapeutic activity, and forming a covalent bond between said reactive group and a reactive functionality on a blood component to

form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity.

Dependent claims are directed to forming the peptide-blood component conjugate *in vivo* or *ex vivo*, forming the conjugate using a maleimide reactive group, coupling reactive group to the peptide via a lysine and/or linking group, coupling the peptide to albumin, and coupling a synthetic peptide to the blood component. The dependent claims further comprise modifying the therapeutic peptide in the less therapeutically active region.

2. The Prior Art

Pouletty *et al.* teach extending *in vivo* lifetimes of physiologically active agents by associating those agents with longer-lived blood component (Abstract). A reactive species bonds to a long-lived blood component. By association with the long-lived blood component, the life of the therapeutic agent is thus increased. The reference also teaches limiting the biological effects of agents present in the mammalian blood stream. Finally, Pouletty *et al.* teach guiding a pharmacologically active or toxic compound attached to a blood component toward, or away from, specific organs (Pouletty *et al.*, page 9 line 32 through page 11, line 1).

Pouletty *et al.* fail to teach a method of protecting a therapeutic peptide from peptidase degradation (as in independent claims 7 and 15). Further, Pouletty *et al.* fail to disclose coupling the reactive group to a less therapeutically active region of a therapeutically active peptide (as in independent claim 15). Further, the reference fails to teach synthetic amino acids as required by claims 14 and 25.

Oppenhelm *et al.* teaches SEQ ID NO: 1032. The reference, however, fails to disclose a method protecting a therapeutic peptide from peptidase degradation, or a method of coupling a reactive group to a less therapeutically active region.

3. The Office's Rejection

The Office argues that that Pouletty *et al.* teach a composition comprising a first conjugate for use in a method for the extended presence of a target binding member in the blood stream of a mammalian host. The Office further asserts that the target-binding agent binds to a target that is a physiologically active agent which may be present in the blood stream of the host. The Office further argues that a first conjugate comprising an anchor and a first member of a specific pair binder are administered to a host. The anchor binds specifically to a long-lived blood associated protein or is a reactive functionality which covalently bonds to a long-lived blood associated protein. The Office also argues that serum albumin is disclosed as a long-lived blood associated protein, and the anchor comprises N-hydroxy-succinimide ester. The conjugate may be administered *in vivo* or *ex vivo*. Finally, the Office asserts that Pouletty *et al.* disclose a method of analyzing the peptide-blood component, and that the target binding member may provide for a wide variety of functions.

Notably, Pouletty *et al.* fails to mention protecting a peptide from peptidase degradation or binding a peptide in a less therapeutic region. The Office admits that the reference lacks specific teachings on amino acid length and SEQ ID NO: 1032.

The Office contends that Oppenhelm *et al.* (U.S. Patent No. 5,837,247) teach chemoactive agents for T-cells. The Office further contends that the reference teaches a defensin protein having the sequence taught by SEQ ID NO: 1032 for inducing or stimulating T-cell chemotaxis in a mammalian subject.

The Office concludes that it would have been obvious for one of ordinary skill in the art to substitute SEQ ID NO: 1032 for the second conjugate protein of Pouletty *et al.* because a) Pouletty *et al.* allegedly teach their invention for extending the *in vivo* lifetimes of

physiologically active agents and SEQ ID NO: 1032 is a physiologically active agent, and b) Pouletty *et al.* allegedly teach that malignant cells are targets for their therapeutic conjugates and SEQ ID NO: 1032 allegedly targets malignant cells.

4. The Prior Art Distinguished

The Office fails to satisfy the requirements to establish a *prima facie* case on multiple grounds. Specifically, the cited prior art references a) fail to teach or suggest all claim limitations of the present invention, b) fail to provide motivation or suggestion for one of ordinary skill in the art to make the claimed invention, and c) fail to disclose any information indicating that one of ordinary skill in the art would have a reasonable chance of success. Accordingly, the subject matter of the instant claims as a whole would not have been obvious to one of skill in the art at the time the invention was made.

First, Pouletty *et al.* in combination Oppenhelm *et al.* fail to teach every element of the claimed invention.

Terminology in the preamble that limits the structure of the claimed invention must be treated as a claim limitation. See, e.g., *Corning Glass Works . v. Sumitomo Elect. U.S.A. Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989). In this application, the claims are limited to "a method of protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*." Since the claims are limited to protecting therapeutic peptides from peptidase degradation, the prior art must meet the limitation of protecting the peptides from peptidase degradation.

Pouletty fails to teach, suggest, or provide the vaguest hint at a method of protecting a therapetic peptide against peptidase degradation. In fact, Pouletty *et al.* disclose a completely different method from that of the claimed invention. The reference teaches extending the *in vivo*

half-life of a physiologically active agent, such as a peptide, as taught in WO 95/10302. It is well known that peptides generally have an extremely short half-life *in vivo*. In Pouletty *et al.*, the half life is extended because the peptide derivative covalently bonds to blood components, which significantly reduces the metabolization action of the liver and/or a drastic reduction of excretion by the kidneys. This concept is therefore applicable to both peptides susceptible and non-susceptible to peptidase degradation.

The method claimed in the instant invention, however, is different from that disclosed by Pouletty *et al.* The instant application claims a "method of protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*." As stated in the application, it has unexpectedly been found that the coupling of the peptide covalently to a blood component such as serum albumin and renders it less susceptible to peptidase degradation *in vivo*. Pouletty *et al.* fail to make any mention of protecting peptides against peptidase degradation.

In addition, Pouletty *et al.* fail to disclose a method including the step of modifying the peptide at a less therapeutically active region, as claimed in independent claim 15. Pouletty *et al.* instead only teach extending *in vivo* lifetimes by non-specific association with a longer-lived species. Pouletty *et al.* fail to teach identifying a therapeutically active region of the peptide.

Oppenhelm *et al.* fail to compensate for the Pouletty's shortcomings. Oppenhelm *et al.* are concerned with defensin proteins. Oppenhelm *et al.* fail to mention, suggest or imply that the disclosed defensin peptides may be protected against peptidase degradation. In addition, Oppenhelm *et al.* fail to mention, suggest or imply that the disclosed defensin peptides may be chemically modified to form peptidase-stabilized defensin derivatives. Finally, Oppenhelm *et al.*

fail to teach either identifying a therapeutically active region of the peptide, or modifying the less therapeutically active region.

Finally, the references fail to teach limitations of dependent claims 14 and 25. Specifically, the Oppenhelm *et al.* fails to teach that one or more of the amino acids in SEQ ID NO:1032 are synthetic. Pouletty *et al.* also fails to teach such a modification. Accordingly, the Office has failed to meet all limitations of claims 14 and 25.

Second, the references, separately or in combination, fail to provide the requisite motivation to combine their teachings to make the claimed invention. Specifically, neither Pouletty *et al.* nor Oppenhelm *et al.* provide one of ordinary skill in the art with the requisite motivation to protect a therapeutic peptide from peptidase degradation *in vivo*, or to modify the peptide by identifying the therapeutic region and modifying the peptide at the less therapeutic portion.

The Office contends that it would have been obvious for one of ordinary skill in the art to substitute SEQ ID NO: 1032 for one of the conjugate protein Pouletty *et al.* because a) Pouletty et al. teach their invention for extending the *in vivo* lifetimes of physiologically active agents and SEQ ID NO: 1032 is a physiologically active agent, and b) Pouletty *et al.* teach that malignant cells are targets for their therapeutic conjugates and SEQ ID NO: 1032 allegedly targets malignant cells. First, the Pouletty *et al.* reference discloses only extending *in vivo* half-lives. Pouletty *et al.*, however, fail to teach that any peptide, including SEQ ID NO: 1032, is susceptible to, or may be protected from, peptidase degradation. Second, the fact that malignant cells are targets for therapeutic conjugates does not mean that one of skill in the art would modify SEQ ID NO. 1032. Third, Pouletty *et al.* provides no disclosure of a identifying the therapeutic region of a peptide and modifying the less therapeutic region as claimed in claim 15

of the instant invention. Consequently, one of ordinary skill in the art would not have been motivated to either identify the therapeutic region, or modify the less therapeutic region, of the peptide.

Oppenhelm *et al.* also fail to provide the requisite motivation for combining the cited prior art references. The Oppenhelm reference is only concerned with defensins. Oppenhelm *et al.* lack any disclosure of protecting the defensins from peptidases, modifying the defensins with a reactive group, modifying the defensins at a less therapeutically active region, or covalently bonding the defensins to a blood component.

Third, the combined prior art references provide no reasonable expectation that the combination would have a reasonable chance of success. Nothing in either Pouletty *et al.* nor Oppenhelm *et al.* indicates that only attachment of therapeutic peptides would constitute a "method of protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*," as claimed in the instant invention. One of ordinary skill in the art would have to assume that a) SEQ ID NO:1032 is sensitive to peptidase degradation, b) it may be modified by coupling to a reactive group, c) it is less susceptible to peptidase degradation after covalent attachment to a blood component, or d) it may be modified in the less therapeutically active region. Neither reference, however, suggests that SEQ ID NO:1032 is susceptible to peptidase degradation, as required by the claims. Neither reference teaches that SEQ ID NO:1032 may be modified by coupling to a reactive group. Neither reference suggests that SEQ ID NO:1032 would be less susceptible to peptidase degradation, if susceptible at all, after covalent attachment to a blood component. Finally, neither reference suggests that SEQ ID NO:1032 may be modified in its less therapeutically active region. Accordingly, neither

reference teaches, suggests, or hints that one of ordinary skill in the art would succeed in making the claimed invention.

In view of the above arguments and claim amendment, Applicants respectfully request that the rejection be withdrawn.

Unexpected Results

The Office has asserted that the data presented on pages 92-181 of the Specification do not establish that the claimed invention is unexpected. In particular, the Office has asserted that the data "merely demonstrate the effectiveness of the instant peptide against peptidases," which is "an expected result based on the cited prior art."

As noted, the Office has failed to provide any evidence that the cited references teach a protecting therapeutic peptides from peptidase degradation, or modifying the peptide in a less therapeutically active region. Further, the Examiner has not pointed to a suggestion or motivation to alter the teachings of the prior art, or that one of ordinary skill would have an expectation of success. Therefore, the Office has not met its burden, and Applicants are not required to show unexpected results.

Protecting peptides from peptidase degradation was a significant problem prior to the instant invention. Attempts have been made to modify the peptide sequence in the therapeutically active region by changing one or more amino acid residue in the sequence, or by making *ex vivo* conjugates, conventionally for example with polyethylene glycol (PEG). Such approaches however generally result in either loss or significant lowering of the therapeutic activity, or no changes towards the peptidase degradation action.

Surprisingly and unexpectedly, it has now been found that by chemically modifying a peptide sequence in accordance with the present method, one may obtain a peptide sequence

which, after covalent bonding to a blood component, is no longer degraded by peptidases as quickly as native peptides. Therapeutic peptides therefore maintain their activity for longer periods. The covalent bonding to the blood component may take place either *in vitro*, or *in vivo*. These dramatic and highly beneficial effects could not have been foreseen by the prior art relied upon by the Examiner.

Conclusion

In light of the above amendments and remarks, Applicant believes that this case is now in condition for allowance. Should there be any remaining issues that remain unresolved, the Office is encouraged to telephone the undersigned.

Attached hereto is a marked up version showing the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made.**" A deleted item is indicated by crossing out the item, e.g., ~~and~~, while an insertion is underlined.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 500862002300. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 25, 2002 By: Michael R. Ward

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please CANCEL claims 1-5.

7. (Twice Amended) A method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a carboxy terminus and an amino terminus and a carboxy terminal amino acid and an amino terminal amino acid, comprising:

(a) modifying said peptide by coupling a reactive group to the carboxy terminal amino acid, to the amino terminal amino acid, or to an amino acid located between the amino terminal amino acid and the carboxy terminal amino acid~~, the reactive group being capable of forming a covalent bond *in vivo* with a reactive functionality on a blood component~~; and

(b) forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase degradation.

15. (Twice Amended) A method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a therapeutically active region of amino acids and a less therapeutically active region of amino acids, comprising:

(a) identifying said therapeutically active region of amino acids;

(b) modifying said peptide at an amino acid included in said less therapeutically active region by coupling thereto a reactive group to said amino acid to form a modified peptide, such that said modified peptide has therapeutic activity~~, the reactive group being capable of forming a covalent bond *in vivo* with a reactive functionality on a blood component~~; and

(c) forming a covalent bond between said reactive ~~entity~~ group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity.